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Effects of Long-Term Bosentan in Children With Pulmonary Arterial Hypertension

Erika Berman Rosenzweig, MD,* D. Dunbar Ivy, MD,† Allison Widlitz, MS, PA,* Aimee Doran, RN, MS, CPNP,† Lori R. Claussen, RN,† Delphine Yung, MD,* Steven H. Abman, MD,† Adele Morganti, PHD,‡ Ngoc Nguyen, BS,‡ Robyn J. Barst, MD*

New York, New York; Denver, Colorado; and Allschwil, Switzerland

OBJECTIVES This study investigated the long-term outcome of children with pulmonary arterial hypertension (PAH) treated with bosentan therapy, with or without concomitant prostanoid therapy.

BACKGROUND Bosentan, an oral endothelin ET_A/ET_B receptor antagonist, improves hemodynamics and exercise capacity in adults with PAH; however, limited data are available on its long-term effects in children.

METHODS In this retrospective study, 86 children with PAH (idiopathic, associated with congenital heart or connective tissue disease) started bosentan with or without concomitant intravenous epoprostenol or subcutaneous treprostinil therapy. Hemodynamics, World Health Organization (WHO) functional class, and safety data were collected.

RESULTS At the cutoff date, 68 patients (79%) were still treated with bosentan, 13 (15%) were discontinued, and 5 (6%) had died. Median exposure to bosentan was 14 months. In 90% of the patients (n = 78), WHO functional class improved (46%) or was unchanged (44%) with bosentan treatment. Mean pulmonary artery pressure and pulmonary vascular resistance decreased (64 ± 3 mm Hg to 57 ± 3 mm Hg, p = 0.005 and 20 ± 2 U · m^2 to 15 ± 2 U · m^2, p = 0.01, respectively; n = 49). Kaplan-Meier survival estimates at one and two years were 98% and 91%, respectively. The risk for worsening PAH was lower in patients in WHO functional class I/II at bosentan initiation than in patients in WHO class III/IV at bosentan initiation.

CONCLUSIONS These data suggest that bosentan, an oral endothelin ET_A/ET_B receptor antagonist, with or without concomitant prostanoid therapy, is safe and efficacious for the treatment of PAH in children. (J Am Coll Cardiol 2005;46:697–704) © 2005 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a rare condition characterized by extensive remodeling of the pulmonary vasculature, resulting in right heart failure and death if untreated. In infants and children, the most common forms of PAH include persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension (IPAH, also referred to as primary pulmonary hypertension), and pulmonary hypertension associated with congenital heart disease (CHD) or chronic lung disease (1). In general, the histopathologic changes are similar in children and in adults, although a spectrum of diseases associated with PAH and other clinical differences have been reported (1). Before the introduction of long-term vasodilator therapy, the prognosis for children with IPAH was poor, with a median survival of 0.8 years compared with 2.8 years in adults (2,3). However, in IPAH a greater percentage of children (~40%) than adults (~10%) are acutely responsive to vasodilator testing and can be effectively treated, at least initially, with chronic oral calcium channel blockade (4).

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Continuous intravenous infusion of epoprostenol appears to be at least as effective in children with PAH as in adults with respect to improving hemodynamics and relieving symptoms (4,5). However, intravenous epoprostenol, owing to its delivery system via central venous access, poses a particular challenge for active pediatric patients who may require frequent central venous line replacements because of dislodgement and/or infection (1). Epoprostenol also has a number of side effects (e.g., jaw pain, headache, nausea, diarrhea, foot pain, and leg pain) (6) that, although often not medically significant, adversely affect a child's overall quality of life. Potentially fatal complications include sepsis related to the intravenous delivery system and rebound pulmonary hypertension following acute withdrawal (6). Furthermore, intravenous epoprostenol requires cooperation during its administration, which may be difficult to obtain with children. The prostacyclin analog, treprostinil (administered via continuous subcutaneous infusion), improves

From the *Division of Pediatric Cardiology, New York Presbyterian Hospital, New York, New York; †University of Colorado Health Sciences Center and Pediatric Heart Lung Center, Children's Hospital, Denver, Colorado; and ‡Actelion Pharmaceuticals Ltd., Allschwil, Switzerland. This research was supported by grant number M01 RR00069, General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health; and by Actelion Pharmaceuticals Ltd.

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Abbreviations and Acronyms

b.i.d. = twice daily
CHD = congenital heart disease
CI = cardiac index
IPAH = idiopathic pulmonary arterial hypertension
PAH = pulmonary arterial hypertension
PAPm = mean pulmonary artery pressure
PVRI = pulmonary vascular resistance index
RAPm = mean right atrial pressure
WHO = World Health Organization

exercise capacity and hemodynamics in both adults and children with PAH; however, pain at the site of infusion has frequently been reported (7) and may be especially troublesome for children. Thus, although chronic prostanoid therapy has proven safe and effective in PAH, due to its route(s) of administration (i.e., intravenous or subcutaneous) and side effects, alternative therapies hold particular appeal for pediatric patients. However, although new therapies for PAH produce sustained clinical and hemodynamic improvement in adults (7–9), limited data are available regarding their use in children.

Endothelin (ET) appears to be a key pathogenic mediator in PAH (10,11). ET-1 mediates a variety of cellular processes including hypertrophy, fibrosis, and inflammation, in addition to being a potent vasoconstrictor and vascular smooth-muscle mitogen (12). Endothelin-1 is present in elevated concentrations in the plasma and lung tissue of adult (10,11) and pediatric (13,14) patients with PAH, which may adversely affect the pulmonary vascular bed, providing a rationale for ET receptor antagonism as a targeted approach for the treatment of PAH. Bosentan, an oral endothelin ET_A/ET_B receptor antagonist, improves exercise capacity, hemodynamics, and time to clinical worsening in adult patients with PAH (15,16) as well as survival in IPAH (17). However, data on bosentan therapy for PAH in children are extremely limited. In an open-label study involving 19 children with PAH, the safety and efficacy of bosentan appeared comparable to results previously reported in adult patients with PAH (18). In the present study, clinical experience from two PAH centers involving 86 pediatric patients with PAH (idiopathic, associated with CHD or connective tissue disease) who received bosentan therapy was pooled to assess the safety and long-term effects of bosentan treatment on functional capacity, hemodynamics, and survival in children with PAH. The addition of bosentan to long-term prostanoid therapy was also evaluated.

PATIENTS AND METHODS

Patients. From May 2001 to April 2003, a cohort of 86 pediatric patients (under 18 years of age) with PAH in World Health Organization (WHO) functional classes (as modified by the New York Heart Association [19]) I to IV were treated with bosentan with or without concomitant intravenous epoprostenol or subcutaneous treprostinil therapy at two centers: the New York Presbyterian Hospital in New York, New York; and the Children's Hospital in Denver, Colorado. The guidelines for treatment of the patients with bosentan for both centers are illustrated in Figure 1. Intravenous epoprostenol or subcutaneous treprostinil were added for patients who had clinically significant deterioration despite treatment with bosentan. Pulmonary arterial hypertension was either idiopathic or associated with CHD or connective tissue disease and was defined as PAH with a mean pulmonary artery pressure ≥25 mm Hg at rest, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance ≥3 $U \cdot m^2$. Patients with

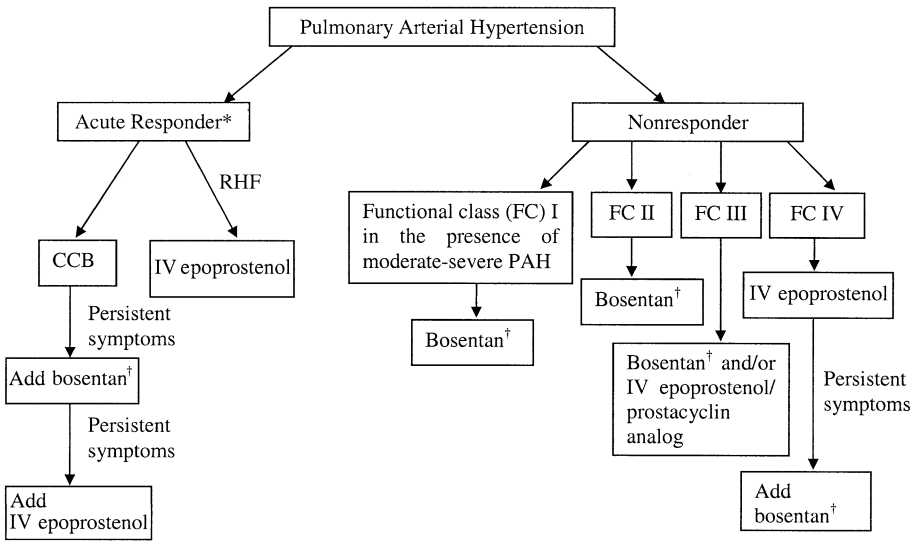

Figure 1. Pediatric Pulmonary Arterial Hypertension (PAH) Treatment Guidelines. *"Acute responder" was defined as: 1) ≥20% decrease in mean pulmonary artery pressure; 2) no change or an increase in cardiac index; and 3) no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance in response to vasodilator testing. †When bosentan became available (April 2001). CCB = calcium channel blockade; RHF = right heart failure.

CHD included those with repaired (n = 19) and unrepaired (n = 25) or partially repaired (n = 4) defects. Twenty-four patients were included in previously published studies (18,20,21). Patients were enrolled following Institutional Review Board approval, informed consent, and assent where appropriate.

Treatment regimen. Bosentan treatment was initiated and dosed according to a previously published regimen (18). The target dose was 31.25 mg twice daily (b.i.d.) for children weighing 10 to 20 kg, 62.5 mg b.i.d. for children weighing 20 to 40 kg, and 125 mg b.i.d. for children weighing >40 kg. Three children weighed <10 kg at bosentan treatment initiation and received 15.6 mg b.i.d. One-half of the target dose was administered daily during the first four weeks of treatment and increased to target dose if bosentan was well tolerated. The dose of concomitant intravenous epoprostenol or subcutaneous treprostinil was adjusted according to the investigators' clinical judgment.

Study assessments. The WHO functional class was assessed by four investigators before starting bosentan treatment and during follow-up at least eight weeks after starting bosentan (patients who died were assigned functional class IV) (Appendix). Patients who were too young to classify (n = 8) were not included in this assessment. Cardiopulmonary hemodynamic parameters (cardiac index [CI], mean pulmonary artery pressure [PAPm], pulmonary vascular resistance index [PVRI], and mean right atrial pressure [RAPm]) were determined by cardiac catheterization within the three-month period preceding bosentan initiation and at least eight weeks after starting bosentan treatment. Acute pulmonary vasoreactivity was assessed with intravenous epoprostenol or inhaled nitric oxide. Acute vasoreactivity was defined as the combination of all three of the following criteria: 1) ≥20% decrease in mean pulmonary artery pressure; 2) no change or an increase in CI; and 3) no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance (22). However, for patients with congenital unrestrictive systemic to pulmonary shunts (e.g., large ventricular septal defect or patent ductus arteriosus), acute vasoreactivity was defined as: 1) ≥20% decrease in pulmonary vascular resistance; 2) no change or an increase in CI; and 3) no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance.

Safety was evaluated by adverse event reports. Clinical and laboratory variables were routinely monitored. Hepatic transaminase levels were checked every two weeks for the first two months and monthly thereafter. In adults, the standard threshold for hepatic transaminase abnormality is >3 times the upper limit of normal (ULN). For pediatric patients, a conservative approach was applied, and hepatic transaminase elevations of >2 times ULN were reported.

Statistical methods. Due to the retrospective nature of the data collection, statistical testing was performed in an exploratory fashion. The observed p values were compared with the standard 0.05 two-sided nominal type I error. The number of patients who improved in WHO functional class from bosentan initiation to last follow-up evaluation was analyzed by McNemar test (class I/II vs. III/IV). Changes from baseline to the last follow-up assessment of hemodynamic variables were analyzed by single-sample *t* test.

Survival, assessed from starting bosentan treatment to death/data cutoff date, was summarized using Kaplan-Meier estimates and 95% confidence limits of the event-free survival at relevant time points.

Multivariate model building based on backward selection process, with a selection level of 0.0157 (23), and the Cox proportional-hazards model were performed to explore the

Table 1. Demographic Characteristics at Bosentan Initiation

		Concomitant Prostanoid	
	All Patients (n = 86)	**Patients Without (n = 42)**	**Patients With (n = 44)**
Male/female, n (%)	37 (43%)/49 (57%)	16 (38%)/26 (62%)	21 (48%)/23 (52%)
Age, yrs [range]			
At bosentan initiation	11 ± 5 [0*–18]	10 ± 6 [0*–18]	12 ± 4 [4–18]
At diagnosis	5 ± 5 [0†–16]	5 ± 5 [0‡–15]	5 ± 5 [0†–16]
Weight, kg [range]	34 ± 16 [5–89]	31 ± 16 [5–64]	37 ± 16 [14–89]
Etiology of pulmonary arterial hypertension, n (%)			
Idiopathic	36 (42%)	11 (26%)	25 (57%)
CHD§	48 (56%)	30 (71%)	18 (41%)
Connective tissue disease	2 (2%)	1 (2%)	1 (2%)
CHD status, n			
Repaired	19	15	4
Unrepaired	24	12	12
Residual defect	5	3	2
Acute vasoreactivity‖, n (%)	14 (16%)	8 (19%)	6 (14%)
WHO functional class I/II/III/IV, n (%)¶	6/34/32/6 (8/43/41/8)	2/18/14/4 (5/47/37/11)	4/16/18/2 (10/40/45/5)

Values are number (percentage) of patients or mean ± SD [range]. *Nine months; †1 month; ‡3 months. §Congenital heart defects included atrial septal defect, atrioventricular septal defect, ventricular septal defect, patent ductus arteriosus, transposition of the great arteries, single ventricle, and double inlet left ventricle. ‖Acute vasoreactivity: responsiveness to acute testing with intravenous epoprostenol or inhaled nitric oxide. ¶All patients (n = 78); without prostanoid (n = 38); with prostanoid (n = 40).

CHD = congenital heart disease; WHO = World Health Organization.

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Table 2. Concomitant Medications at Bosentan Initiation

	All Patients (n = 86)	Concomitant Prostanoid*	
		Patients Without (n = 42)	Patients With (n = 44)
CCBs	20 (23%)	18 (43%)	2 (5%)
Anticoagulants	69 (80%)	33 (79%)	36 (82%)
Diuretics	46 (53%)	15 (36%)	31 (70%)
PDE inhibitors	20 (23%)	9 (21%)	11 (25%)
L-arginine	5 (6%)	3 (7%)	2 (4%)
Oxygen as needed	46 (53%)	24 (57%)	22 (50%)

Values are number (percentage) of patients. *At study initiation: intravenous epoprostenol (n = 36); subcutaneous treprostinil (n = 8).
CCBs = calcium channel blockers; PDE = phosphodiesterase.

potential effect of selected risk factors on time to worsening of PAH. Time to PAH worsening was defined as the time from bosentan initiation to the first occurrence of worsening PAH requiring additional or alternative therapy for PAH (intravenous epoprostenol, subcutaneous treprostinil, oral sildenafil) or atrial septostomy, transplantation, or death. The selected risk factors recorded at bosentan initiation included gender, age at diagnosis, etiology (IPAH vs. other), acute pulmonary vasoreactivity (acute responder vs. nonresponder), WHO functional class (class I/II vs. III/IV), monotherapy at bosentan initiation (bosentan with or without concomitant prostanoid therapy), and hemodynamic variables (CI, PAPm, PVRI, and RAPm). When we investigated the effects of potential risk factors that have been measured on a quantitative scale, we categorized the value of these factors in two groups using the observed mean as a cutoff point. Sensitiveness analysis was performed by applying the backward selection process and considering all selected risk factors except hemodynamic variables, which were assessed in only 62 patients. In addition, the model-building process was applied, including all the factors that were significant at the 0.1 level in the univariate Cox regression (24).

RESULTS

A cohort of 86 children with PAH started bosentan therapy between May 2001 and April 2003, with follow-up through August 2003. The median exposure time to bosentan up to the cutoff date of August 2003 was 14 months (range 2 to 28 months).

Demographic characteristics at bosentan initiation. Demographic characteristics at bosentan initiation are shown in Tables 1 and 2. Patients ranged in age from 9 months to 18 years (11 ± 5 years; mean ± SD) at the start of bosentan therapy and were 5 ± 5 years (mean ± SD) of age at the time of PAH diagnosis. The subgroups of patients who started bosentan with or without concomitant prostanoid therapy (intravenous epoprostenol or subcutaneous treprostinil) at bosentan initiation had somewhat different characteristics. In the subgroup starting bosentan without prostanoid therapy, PAH associated with CHD was more frequent than IPAH, and the percentage of repaired congenital heart defects was also higher. The subgroups also differed in concomitant treatment with calcium channel blockers (i.e., 43% of patients in the subgroup starting bosentan without concomitant prostanoid therapy were being treated with calcium channel blockade therapy versus 5% in the subgroup with concomitant prostanoid therapy). At bosentan initiation, although functional class distribution was similar in both groups, hemodynamic parameters were consistent with more severe disease in the subgroup starting bosentan with concomitant prostanoid therapy (Table 3). At bosentan initiation, in the subgroup already receiving concomitant prostanoid therapy, median exposure to intravenous epoprostenol was 48 months (range 2 days to 115 months) and median exposure to subcutaneous treprostinil was 31 months (range 19 to 41 months).

WHO functional class. Seventy-eight patients (38 in the subgroup starting bosentan without concomitant prostanoid therapy and 40 in the subgroup with concomitant prostanoid therapy) had WHO functional class assessments at

Table 3. Cardiopulmonary Hemodynamic Parameters at Bosentan Initiation and After at Least Eight Weeks of Treatment With Bosentan

	All Patients (n = 49)		Concomitant Prostanoid			
			Patients Without (n = 25)		Patients With (n = 24)	
	Baseline	Change	Baseline	Change	Baseline	Change
PAPm (mm Hg)	64 ± 3	−7 ± 2*	59 ± 3	−9 ± 3*	68 ± 5	−4 ± 3
PCWPm (mm Hg)†	9 ± 1	1 ± 1	9 ± 1	0 ± 1	9 ± 1	2 ± 1
RAPm (mm Hg)	7 ± 1	0 ± 1	6 ± 0.4	1 ± 1	8 ± 1	0 ± 1
CI† (l/min/m^2)	3.8 ± 0.2	0.0 ± 0.2	3.7 ± 0.3	−0.1 ± 0.3	3.9 ± 0.3	0.1 ± 0.4
PVRI (U · m^2)	19 ± 2	−4 ± 2*	18 ± 2	−5 ± 1*	21 ± 3	−3 ± 3
SVRI† (U · m^2)	21 ± 1	−2 ± 1	21 ± 2	−3 ± 2	20 ± 2	−2 ± 2
PVRI/SVRI†	0.9 ± 0.1	−0.1 ± 0.1	0.8 ± 0.1	−0.2 ± 0.1*	0.9 ± 0.1	0.1 ± 0.1
SAPm (mm Hg)	77 ± 2	−5 ± 2	76 ± 3	−5 ± 2	76 ± 3	−6 ± 3

Values are given as mean ± SEM for evaluable patients (i.e., patients with valid assessments at study initiation (baseline) and after at least 8 weeks of treatment with bosentan, n = 49). *$p < 0.05$ (single-sample t test). †All patients (n = 45); without prostanoid (n = 23); with prostanoid (n = 22).
CI = cardiac index; PAPm = mean pulmonary artery pressure; PCWPm = mean pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance index.

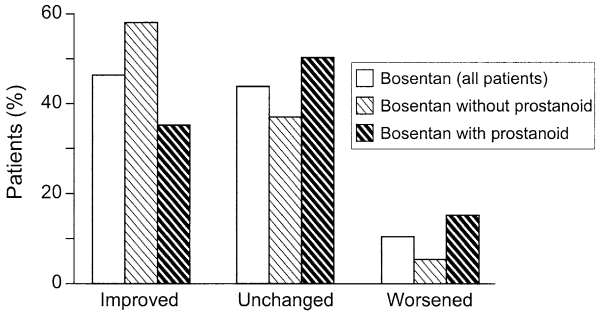

Figure 2. World Health Organization functional class at bosentan initiation and after at least eight weeks of treatment with bosentan. (Patients who died were assigned functional class IV.)

bosentan initiation and at follow-up (at least eight weeks after the initiation of bosentan treatment (Appendix). The median follow-up of these patients was 12 months (range 3 to 25 months).

Overall, 36 patients (46%) improved by at least one class ($p < 0.001$; 5 of these improved by 2 functional classes), 34 patients (44%) remained in the same functional class, and 8 (10%) worsened by one class (Fig. 2). Although not statistically significant, the improvement appeared more pronounced for the patients who started bosentan without concomitant prostanoid therapy than for those treated with bosentan and concomitant prostanoid therapy.

Cardiopulmonary hemodynamics. Forty-nine patients (25 in the subgroup starting bosentan without concomitant prostanoid therapy and 24 in the subgroup with concomitant prostanoid therapy) had hemodynamic assessments within the three-month period preceding bosentan initiation and at follow-up (i.e., at least eight weeks after the initiation of bosentan treatment) (Table 3). The median follow-up of these patients was 9 months (range 3 to 28 months). Overall, PAPm decreased from 64 ± 3 mm Hg to 57 ± 3 mm Hg (mean ± SEM, n = 49; p = 0.005). Pulmonary vascular resistance decreased from 20 ± 2 $U \cdot m^2$ to 15 ± 2 $U \cdot m^2$ (mean ± SEM, n = 49; p = 0.01); CI was unchanged. For the children receiving bosentan without concomitant prostanoid therapy versus the patients receiving bosentan with concomitant prostanoid therapy, PAPm decreased −9 ± 3 mm Hg versus −4 ± 3 mm Hg (mean ± SEM) and PVRI decreased −6 ± 1 $U \cdot m^2$ versus −3 ± 3 $U \cdot m^2$ (mean ± SEM), respectively.

Treatment status and survival. Sixty-five (76%) of the 86 children were followed for at least one year. Patient survival and treatment status after one year of treatment with bosentan are shown in Figure 3. Among the 33 patients who started bosentan without concomitant prostanoid therapy at bosentan initiation and were followed for at least one year, 25 (76%) continued bosentan without requiring additional therapy, 4 (12%) continued bosentan with additional PAH treatment started (3 intravenous epoprostenol, 1 oral sildenafil), 3 (9%) discontinued bosentan, and 1 (3%) died. Among the 32 patients who started bosentan with concomitant prostanoid therapy at bosentan initiation and were

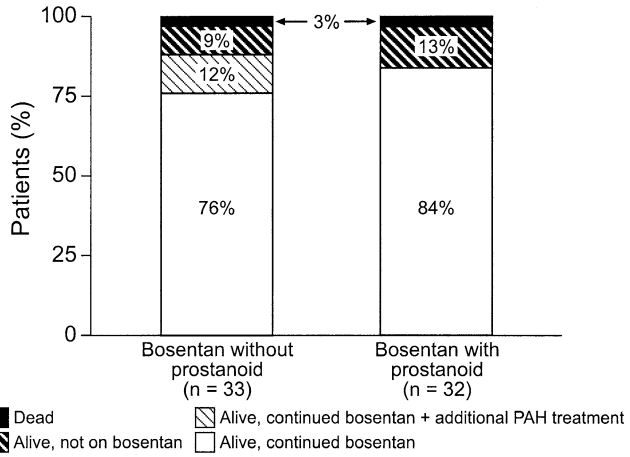

Figure 3. Patient survival and treatment status at one year of treatment with bosentan (i.e., these patients were started before August 2002; >1 year before the data cutoff date, August 2003).

followed for at least one year, 27 (84%) continued bosentan, 4 (13%) discontinued bosentan, and 1 (3%) died. The other three patients who died started receiving bosentan after August 2002, which was <1 year before the data cutoff of August 2003 (i.e., they were followed and treated for less than one year), making long-term assessment difficult.

At data cutoff date, 68 of the 86 patients (79%) continued bosentan. Eleven of these 68 patients received additional PAH treatment (intravenous epoprostenol, oral sildenafil, or atrial septostomy): 10 patients had failed treatment with bosentan and 1 patient had oral sildenafil added despite doing well clinically. Thirteen of the 86 patients (15%) discontinued bosentan because of: increase in hepatic transaminases (n = 3), other adverse events (n = 4), or treatment failure (alternative PAH treatment or transplantation; n = 6). Five of the 86 patients (6%) died (Table 4). Patient survival and treatment status in both subgroups were comparable. Overall, the dose for the 36 children treated with concomitant intravenous epoprostenol decreased from

Table 4. Patient Survival and Treatment Status at Data Cutoff Date

	All Patients (n = 86)	Concomitant Prostanoid	
		Patients Without (n = 42)	Patients With (n = 44)
Continued bosentan treatment, n (%)	68 (79%)	35* (83%)	33† (75%)
Discontinuation, n (%)			
Increase in liver enzymes	3 (3%)	2 (5%)	1 (2%)
Other adverse event	4 (5%)	2 (5%)	2 (4%)
Treatment failure‡	6 (7%)	1 (2%)	5 (11%)
Deaths, n (%)	5 (6%)	2 (5%)	3 (7%)

Values are number (percentage) of patients. *Six patients were considered treatment failure and required additional treatments (intravenous epoprostenol or oral sildenafil). †Five patients received additional treatments: 4 patients were considered treatment failure (atrial septostomy or oral sildenafil), 1 patient received oral sildenafil to optimize therapy. ‡Treatment failure: requiring additional or alternative treatment (i.e., intravenous epoprostenol, oral sildenafil, atrial septostomy, or transplantation).

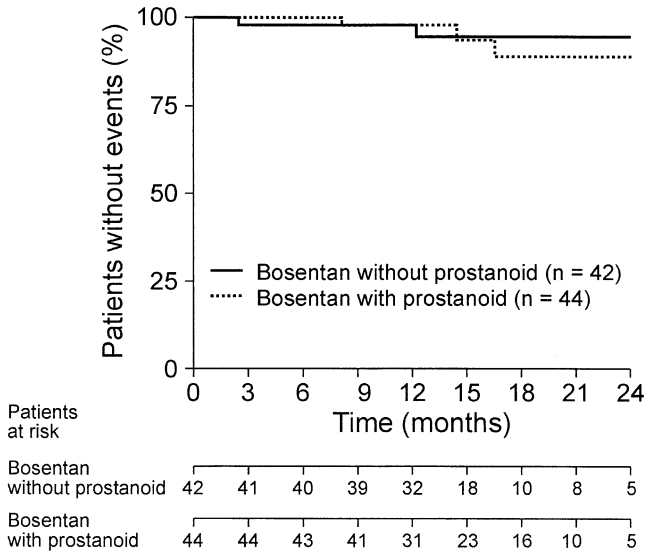

Figure 4. Kaplan-Meier estimates of survival. Median survival follow-up was 15 months (range 3 to 28 months) in the entire bosentan-treated group, 15 months (range 3 to 28 months) in the bosentan subgroup without concomitant prostanoid therapy, and 16 months in the bosentan subgroup with concomitant prostanoid therapy (range 5 to 27 months).

73 ± 42 ng/kg/min (mean ± SD) at bosentan initiation to 68 ± 43 ng/kg/min at data cutoff date; the dose for the 8 patients treated with concomitant subcutaneous treprostinil was 59 ± 26 ng/kg/min (mean ± SD) at bosentan initiation and 59 ± 32 ng/kg/min at data cutoff date.

Summary statistics on survival for the 86 patients are shown in Figure 4. Kaplan-Meier estimates of survival at one and two years were 98% and 91%, respectively. In the subgroup starting bosentan without concomitant prostanoid therapy, the one- and two-year survival estimates were 98% and 94%, respectively, whereas in the subgroup receiving concomitant prostanoid therapy, the one- and two-year survival estimates were 98% and 89%, respectively. In the subgroup of patients with IPAH (with and without concomitant prostanoid therapy), the one- and two-year survival estimates were 100% and 88%, respectively, whereas in the subgroup with PAH associated with CHD (with and without concomitant prostanoid therapy), the one- and two-year survival estimates were the same at 96%.

Safety and tolerability. The most frequent adverse event was peripheral edema (n = 7, 8%). Systemic hypotension was reported in three patients (3%). Fatigue leading to discontinuation was observed in two patients (2%) 9 and 11 months after starting bosentan, which resolved following discontinuation of bosentan, and two patients (2%) with unrepaired CHD discontinued bosentan 5 and 7 months after starting bosentan because of systemic arterial oxygen desaturation. The systemic arterial oxygen saturation returned to baseline following discontinuation of bosentan in one of these two patients.

Asymptomatic increases in liver transaminases (above 2× ULN) were reported in 10 patients (12%). No patients had symptomatic increases in liver transaminases. Of the 10 patients who had asymptomatic increases in liver transaminases, 7 (8%) had an elevation of two to three times ULN (2 of the 7 patients discontinued bosentan), 1 (1%) had an elevation three to five times ULN, and 2 (2%) had an elevation five to eight times ULN (1 patient discontinued bosentan). The elevation in liver transaminases resolved in the seven patients (8%) that continued treatment with bosentan.

Five patients died during the study. Three patients in the subgroup starting bosentan with concomitant prostanoid therapy died: two from hemoptysis and acute respiratory distress syndrome, and one from worsening right heart failure. Two patients in the subgroup starting bosentan without prostanoid therapy died from right heart failure. All deaths were considered as due to the clinical progression of PAH.

Risk factors associated with the time to PAH worsening. Table 5 summarizes the results of the multivariate analysis of the effect of selected risk factors assessed at bosentan initiation on time to PAH worsening. Two separate models with a backward selection level of 0.0157 were performed including (n = 81) or excluding (n = 62) the patients without hemodynamic assessments at bosentan initiation. The hazard ratios obtained from each model (with and without hemodynamics) were similar, and the inclusion of hemodynamic parameters led to the selection of the same prognostic factor (i.e., WHO functional class). The proportional risk of PAH worsening was higher for patients in WHO functional classes III and IV at bosentan initiation than in patients in WHO class I/II at bosentan initiation, but was not found to be significantly influenced by gender, age at diagnosis, etiology, acute vasoreactivity, bosentan monotherapy, or hemodynamic variables. In the univariate selection process (Table 6), WHO functional classes III and IV at bosentan initiation and older age at diagnosis were identified for the final model. Although the hazard ratio of WHO functional class was comparable to the one observed

Table 5. Multivariate Analysis Relating Time to PAH Worsening to Risk Factors

	Model 1 (n = 81)		Model 2 (n = 62)	
Risk Factor	**Hazard Ratio [95% CI]**	**p Value**	**Hazard Ratio [95% CI]**	**p Value**
WHO functional class III to IV	7.33 [2.16–24.90]	0.001	7.26 [1.64–32.23]	0.009
Model fit	Number of events = 21 Wald test p = 0.001		Number of events = 15 Wald test p = 0.009	

CI = confidence interval; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

Table 6. Cox Modeling Based on Risk Factors Selected in the Univariate Selection Process on Time to PAH Worsening

	Final Adjusted Model (n = 81)*		Unadjusted Models†	
Risk Factor	**Hazard Ratio [95% CI]**	**p Value**	**Hazard Ratio [95% CI]**	**p Value**
WHO functional class III to IV	6.76 [1.96–23.31]	0.0025	7.33 [2.16–24.90]	0.0014
Age at PAH diagnosis	1.47 [0.62–3.50]	0.39	2.12 [0.90–5.00]	0.09

*The final adjusted model including WHO functional class III–IV and age at PAH diagnosis >5 years includes 21 events; p = 0.0042. †Unadjusted models are univariate models including one single covariate at a time.
CI = confidence interval; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

in the backward selection modeling, age at diagnosis was no longer statistically significant in the multivariate analysis.

DISCUSSION

Pulmonary arterial hypertension is a progressive disease associated with a poor prognosis in both children and adults (3,4,25). Despite increased knowledge regarding the natural history and clinical course of adult patients with PAH (1), data describing the response to treatment, including survival in pediatric PAH patients, are limited. The present study was a retrospective analysis of clinical data that involved a large cohort of children with PAH (IPAH or PAH associated with CHD or connective tissue disease), thereby providing a fairly extensive experience of long-term safety and efficacy of bosentan for the treatment of pediatric PAH with or without concomitant prostanoid treatment.

Among the 78 pediatric patients with baseline and follow-up WHO functional class assessments, 70 patients (90%) either improved (36 patients, 46%) or were unchanged (34 patients, 44%) as assessed by WHO functional class, consistent with clinical benefit for the overall population treated with bosentan. The observed improvement in hemodynamic parameters was similar to that previously reported in a small, 12-week open-label study with bosentan in children with IPAH or PAH associated with CHD (excluding patients with the classic Eisenmenger syndrome) (18). The improvements in WHO functional class and hemodynamics were more pronounced for the children who started bosentan without concomitant prostanoid therapy than for those treated with bosentan and prostanoid therapy. However, the patients who needed prostanoid treatment before bosentan initiation appeared to have more advanced disease, as suggested by their hemodynamic parameters at bosentan initiation. For these children, additional benefit with bosentan may have been lessened by previous improvement with prostanoid therapy.

Children with PAH often have a different hemodynamic profile and response to treatment than adults. As observed in other pediatric studies (3), the PAH children in this study had a higher CI at bosentan initiation compared with their adult counterparts. This may account for the lack of increase in CI with treatment with bosentan, which is in contrast with the increase in CI reported for adult PAH patients (15,26). However, PAPm, which tended to be higher at baseline for children with PAH than for adults with PAH, improved with bosentan treatment to a greater degree in children than in previous reports with adult patients (15,26).

The safety profile of bosentan in children with PAH was similar to that previously reported with adult patients (15,26). However, there were also two cases of fatigue and two cases of systemic arterial oxygen desaturation, with both cases of desaturation occurring in patients with unrepaired congenital heart defects.

As the dose of intravenous epoprostenol was adjusted based on the clinical investigator's discretion, whether it can be reduced in combination with bosentan could not be determined from this retrospective study. However, this has been previously reported (20) for eight IPAH children included in the present study who were in stable condition on intravenous epoprostenol for more than one year. The addition of bosentan therapy allowed for a reduction of the intravenous epoprostenol dose, which decreased epoprostenol-associated side effects without apparent clinical or hemodynamic worsening. In three of these children, with the addition of bosentan, the epoprostenol was discontinued with maintenance of hemodynamics for up to one year. In a recent study with adult PAH patients (21), the combination of oral bosentan and intravenous epoprostenol therapy was evaluated in comparison with intravenous epoprostenol alone. Unfortunately, perhaps because of the small sample size, statistically significant differences were not observed. In practice, although bosentan and intravenous epoprostenol have been prescribed simultaneously, additional clinical data are necessary to evaluate the overall safety and efficacy of the combination (27).

The present study reports survival rates after one and two years of bosentan treatment with or without concomitant prostanoid therapy (respectively 98% and 91% for all etiologies, 100% and 88% for IPAH, and 96% at one and two years for PAH-CHD). In the present study, PAH worsening was strongly related to WHO functional class at bosentan initiation, independent of PAH etiology. Patients in WHO functional classes I and II at the start of bosentan therapy had a markedly lower occurrence of PAH worsening than did patients in functional classes III and IV at the start of bosentan therapy. In several IPAH studies, WHO functional classes III and IV have been associated with a decreased survival rate in both pediatric and adult PAH patients (2,3). Because a clinical deterioration is often

combined with a deteriorating hemodynamic status, it is not surprising that the addition of hemodynamic variables did not significantly improve the model fit.

Although the risk for PAH worsening was significantly associated with age at diagnosis by univariate analysis (i.e., the younger the child was at the time of diagnosis, the better the outcome was), the age at diagnosis was no longer significant once functional class was included in the model. Greater pulmonary vascular medial hypertrophy with less intimal fibrosis and fewer plexiform lesions have been reported in young children in comparison to older PAH patients (22). In addition, younger children have also been reported to acutely respond with vasodilator testing more often than adult IPAH patients (3,4).

The main limitations of this study are its retrospective design and the lack of a control group. However, considering the limited clinical pediatric data currently available, the present retrospective study, which involves a large cohort of children, provides clinical data consistent with long-term safety and efficacy of bosentan for the treatment of pediatric PAH. The inclusion of patients with different PAH etiologies (IPAH and PAH associated with CHD or connective tissue disease) could also be considered a limitation. However, these clinical conditions are known to share many histopathologic, pathobiologic, and clinical similarities (19). Although the median follow-up for hemodynamics was nine months and does not necessarily constitute "long-term" follow-up, we believe these data are meaningful given the lack of previous hemodynamic data in children. Furthermore, whereas the efficacy of bosentan in patients with IPAH has been demonstrated in adults (16), limited clinical data are available on the treatment of patients with PAH associated with CHD. The data from the present study, which include a large proportion of patients with PAH associated with CHD, suggests that bosentan may also benefit these patients.

In conclusion, these data suggest that bosentan, an oral endothelin ET_A/ET_B receptor antagonist, with or without concomitant prostanoid therapy, is safe and efficacious for the treatment of PAH in children.

Reprint requests and correspondence: Dr. Erika Berman Rosenzweig, Division of Pediatric Cardiology, New York Presbyterian Hospital, 3959 Broadway, BHN 2-255, New York, New York 10032. E-mail: esb14@columbia.edu.

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APPENDIX

For the WHO Functional Classification of Pulmonary Hypertension, please see the online version of this article.